DESCRIPTION

PROCESS FOR THE PREPARATION OF OXAZOLE DERIVATIVES

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TECHNICAL FIELD

The present invention relates to an industrially advantageous production method for forming a carbon-carbon bond at the 5-position of oxazole.

BACKGROUND ART

There are various production methods (e.g. WO97/36882) of compounds having a carbon substituent (a group bonded via a carbon) bonded at the 5-position of oxazole. Most of them require introduction of a necessary carbon substituent before constructing an oxazole ring. However, the starting material usable for the production method is limited and the synthesis thereof is associated with difficulty.

In view of the above, the development of an easy and simple method for introducing a carbon substituent into the 5-position of oxazole is highly significant, and finding of a reaction permitting direct formation of a carbon-carbon bond on an oxazole having no substituent at the 5-position is extremely significant.

DISCLOSURE OF INVENTION

The present inventors have conducted intensive studies in an attempt to introduce a carbon substituent into the 5-position of oxazole and found for the first time that a reaction of an oxazole having no substituent at the 5-position (particularly one having an oxo group or amino group at the 2-position) with olefin in the presence of an acid or base unexpectedly results in an easy reaction with the olefin and the formation of a carbon-carbon bond at the 5-position of the oxazole, based on which they investigated further and completed the present invention.

Accordingly, the present invention relates to:

(1) a method of producing a compound represented by the

NMR($CDCl_3$): 2.70(2H, t, J=7.0Hz), 2.98(2H, t, J=7.0Hz), 3.65(3H, s), 7.42(5H, s), 10.37(1H, s)

Example 2

4-(4-Phenyl-2-oxo-4-oxazolin-5-yl)-4-phenyl-2-butanone

To a solution of 4-phenyl-2-oxo-4-oxazoline (1.61 g) and benzalacetone (1.46 g) in acetonitrile (20 ml) was added dropwise methanesulfonic acid (0.96 g). After stirring the obtained mixture at room temperature for 30 min, water was added, and the mixture was extracted with ethyl acetate. The extract was washed with water and dried ($MgSO_4$), and the solvent was evaporated. The residue was subjected to silica gel column chromatography and eluted with hexane-ethyl acetate (1:1). The solvent was evaporated. Crystallization from isopropyl ether gave 4-(4-phenyl-2-oxo-4-oxazolin-5-yl)-4-phenyl-2-butanone (2.65 g; yield 86.3%). Recrystallization from ethanol gave colorless crystals.

Elemental analysis value for $C_{19}H_{17}NO_3$

Calculated: C, 74.25; H, 5.58; N, 4.56

Found: C, 74.28; H, 5.72; N, 4.52

NMR($CDCl_3$): 2.16(3H, s), 3.02(1H, dd, J=17.7 and 6.0Hz), 3.34(1H, dd, J=17.7 and 8.4Hz), 4.67(1H, dd, J=8.4 and 6.0Hz), 7.21-7.50(10H, m), 10.10(1H, s)

Example 3

Methyl 2-(4-(4-chlorophenyl)-2-oxo-4-oxazolin-5-yl)propionate

4-(4-Chlorophenyl)-2-oxo-4-oxazoline (3.00 g) and methyl acrylate (1.52 mL) were dissolved in methanol (15 mL), and a solution (0.30 mL) of 28% sodium methoxide (NaOMe) in methanol was added. The obtained mixture was stirred with reflux for 2 h, and the solvent was concentrated under reduced pressure. Toluene (21 mL) and water (21 mL) were added to the residue and the mixture was stirred at room temperature for 1 h. The mixture was cooled to not higher than 5°C and, after stirring for 1

h, the precipitated crystals were collected by filtration, and washed successively with water (21 mL) and isopropyl ether (21 mL). The crystals were dried under reduced pressure at 50°C to give the title compound (2.85 g; yield 66.0%) as pale-purple crystals. The NMR data of the product was identified well with the data of the compound obtained in Example 1.

Example 4

5-(3-Oxo-1-phenylbutyl)-4-phenyl-2-oxo-4-oxazoline

4-Phenyl-2-oxo-4-oxazoline (1.61 g) and benzalacetone (1.46 g) were dissolved in acetonitrile (20 mL), and methanesulfonic acid (0.96 mL) was added. The obtained mixture was stirred at room temperature for 1 h and water (100 mL) and ethyl acetate (100 mL) were added to the reaction mixture. The organic layer was separated, washed twice with water (50 mL), and concentrated under reduced pressure to give an oily substance. The obtained oily substance was subjected to silica gel column chromatography and eluted with n-hexane-ethyl acetate (1:1). The solvent was evaporated and isopropyl ether (50 mL) was added to the obtained oily substance to allow crystallization and the mixture was stirred at room temperature for 1 h. The crystals were collected by filtration and washed with isopropyl ether (20 mL) to give the title compound (2.65 g; yield 86.3%) as white crystals.

Elemental analysis value for $C_{19}H_{17}NO_3$

Calculated: C,74.25 ; H,5.58 ; N,4.56.

Found: C,74.28 ; H,5.72 ; N,4.52.

NMR($CDCl_3$): 2.16 (3H, s), 3.02(1H, dd, J=17.7 and 6.0Hz), 3.34(1H, dd, J=17.7 and 8.4Hz), 4.67(1H, dd, J= 8.4 and 6.0Hz), 7.21-7.50(10H, m), 10.10(1H, s).

Example 5

Methyl 2-(4-(4-methoxyphenyl)-2-oxo-4-oxazolin-5-yl)propionate

4-(4-Methoxyphenyl)-2-oxo-4-oxazoline (1.00 g), methyl acrylate (0.94 mL) was dissolved in toluene (20 mL) and boron trifluoride etherate (1.31 mL) was added. The obtained mixture was heated to 90°C, and after stirring for 2 h, the solvent was concentrated under reduced pressure to give an oily substance. The obtained oily substance was subjected to silica gel column chromatography and eluted with n-hexane-ethyl acetate (1:1). The solvent was evaporated and the obtained oil was crystallized from ethanol. Isopropyl ether (10 mL) was added and the mixture was stirred at not higher than 5°C for 1 h. The crystals were collected by filtration and washed with isopropyl ether to give the title compound (0.30 g; yield 20.7%) as gray-white crystals.

Elemental analysis value for $C_{14}H_{15}NO_5$

Calculated: C,60.64 ; H,5.45 ; N,5.05.

Found: C,60.38 ; H,5.25 ; N,4.99.

NMR($CDCl_3$): 2.68 (2H, t, J=7.7Hz), 2.97(2H, t, J=7.7Hz), 3.67(3H, s), 3.83(3H, s), 6.97 (2H, d, J=8.7Hz), 7.38 (2H, d, J=8.7Hz), 10.13(1H, s).

Example 6

Methyl 2-(4-(4-chlorophenyl)-2-oxo-4-oxazolin-5-yl)propionate

4-(4-Chlorophenyl)-2-oxo-4-oxazoline (3.0 g) was dissolved in methanol (30 mL) and methyl acrylate (1.66 mL) and triethylamine (2.14 mL) were added. The obtained mixture was stirred with reflux for 6 h, and the solvent was concentrated under reduced pressure. Isopropanol (9 mL) and isopropyl ether (21 mL) were added, and the mixture was allowed to stand at room temperature overnight and was cooled to not higher than 5°C and stirred for 1 h. The precipitated crystals were collected by filtration and washed with isopropyl ether to give the title compound (2.81 g; yield 65.0%).

Example 7

4-(4-Chlorophenyl-5-(1-methyl-3-oxobutyl)-2-oxo-4-oxazoline

4-~~[illegible]~~(4-Chlorophenyl)-2-oxo-4-oxazoline (1.0 g) and 3-penten-2-one (0.75 mL) were dissolved in methanol (30 mL), and triethylamine (0.71 mL) was added. The mixture was stirred with reflux for 15 h. The reaction mixture was concentrated under reduced pressure and isopropyl ether (20 mL) was added to allow crystallization. The crystals were collected by filtration and washed with isopropyl ether to give the title compound (1.14 g; yield 79.7%) as pale-yellow-brown crystals.

Elemental analysis value for $C_{14}H_{14}NO_3Cl$

Calculated: C,60.11 ; H,5.04 ; N,5.01.

Found: C,59.84 ; H,5.04 ; N,5.02.

NMR($CDCl_3$): 1.27(3H, d, J=6.9Hz), 2.17(3H, m), 2.71(1H, dd, J=17.9 and 6.3 Hz), 2.96(1H, dd, J=17.9 and 7.6 Hz), 3.51-3.58(1H, m), 7.43-7.51(4H, m), 10.25(1H, s).

Example 8

Methyl 2-amino-4-(4-chlorophenyl)-5-oxazolepropionate

To a solution of 2-amino-4-(4-chlorophenyl)oxazole (584 mg) and methyl acrylate (0.81 mL) in dichloromethane (5.8 mL) was added dropwise titanium tetrachloride ($TiCl_4$) (0.99 mL) under ice-cooling. The obtained mixture was allowed to warm to room temperature and stirred for 6 h. The solvent was evaporated and water was added to the residue. The mixture was extracted with ethyl acetate, and the extract was washed with water and dried ($MgSO_4$). The solvent was evaporated and the residue was crystallized from isopropyl ether-ethyl acetate (209 mg; yield 51.3%). Recrystallization from isopropyl ether-ethyl acetate gave the title compound as pale-yellow crystals.

Elemental analysis value for $C_{13}H_{13}NClN_2O_3$

Calculated: C,55.62 ; H,4.67 ; N,9.98.

Found: C,55.48 ; H,4.52 ; N,10.00.

NMR($CDCl_3$): 2.67(2H, t, J=7.8Hz), 3.09(2H, t, J=7.8Hz),

yl]propionate

A mixture of 4-(3',4'-dichlorophenyl)-2-oxazolone (8.9 g), methyl acrylate (13.2 g), boron trifluoride diethyl ether complex (8.5 g) and toluene (100 mL) was stirred with heating under reflux for 12 h. The reaction mixture was concentrated and poured into iced water (500 mL). The precipitated solid was collected by filtration, washed with water and air-dried to give the title compound as crystals (9.0 g, 75%). Recrystallization from ethyl acetate-hexane gave pale-yellow prism crystals. melting point: 129-130°C.

Reference Example 1

4-(4-Chlorophenyl)-2-oxo-4-oxazoline

To a mixture of ~~4~~ 4'-chloro-2'-hydroxyacetophenone (3.41 g), potassium cyanate (3.25 g) and isopropanol (15 mL) was added dropwise acetic acid (2.88 g) at 50°C. The obtained mixture was stirred at 50°C for 5 h and water (34 mL) was added. The precipitated crystals were collected by filtration, and washed with water and then with isopropyl ether to give 4-(4-chlorophenyl)-2-oxo-4-oxazoline (3.33 g; yield 85.1%).

NMR(DMSO-d_6): 7.50(2H, d, J=8.6Hz), 7.58(2H, d, J=8.6Hz), 7.73(1H, s), 11.39(1H, bs)

Reference Example 2

4-Phenyl-2-oxo-4-oxazoline

In the same manner as in Reference Example 1, the title compound was obtained (yield 64.1%).

NMR($CDCl_3$): 7.13(1H, s), 7.26-7.44(5H, m)

Reference Example 3

2-Amino-4-(4-chlorophenyl)oxazole

To a mixture of 4-chloro-2'-hydroxyacetophenone (17.06 g), cyanamide (5.04 g) and methanol (170 mL) was added dropwise 28% sodium methoxide under ice-cooling. The obtained mixture was allowed to warm to room temperature and stirred for 2 h. Water (34 mL) was added,

. To a mixture of 2-(2-methyl-1-imidazolyl)-4-(4-trifluoromethylphenyl)-5-oxazolepropanol (700 mg), 2-methylphenol (432 mg), tributylphosphine (607 mg) and tetrahydrofuran (10 mL) was added 1,1'-(azodicarbonyl)-dipiperidine (750 mg) at room temperature and the mixture was stirred for 1 h. The reaction mixture was concentrated and the residue was subjected to silica gel column chromatography. The title compound was obtained as crystals from an eluate from ethyl acetate-hexane (2:3, v/v). Recrystallization from acetone-isopropyl ether gave colorless prism crystals (591 mg, 67%). melting point: 101-102°C.

Reference Example 18

2-Hydroxy-3',4'-dichloroacetophenone

A mixture of 2-bromo-3',4'-dichloroacetophenone (78.0 g), sodium formate (68.0 g) and methanol (300 mL) was heated under reflux and stirred for 16 h. The reaction mixture was concentrated and poured into water (1 L). The precipitated solid was collected by filtration, washed with water and then with isopropyl ether, air-dried, and further dried under reduced pressure at 40°C to give the title compound as crystals (25.0 g, 42%). Recrystallization from ethyl acetate-hexane gave pale-yellow prism crystals. melting point: 115-118°C

Reference Example 19

4-(3',4'-Dichlorophenyl)-2-oxazolone

A mixture of 2-hydroxy-3',4'-dichloroacetophenone (10.3 g), potassium cyanate (8.1 g) and 2-propanol (100 mL) was heated to 50°C, and acetic acid (6.0 g) was slowly added dropwise. The mixture was stirred at 50°C for 2 h. The reaction mixture was concentrated and poured into iced water (200 mL). The precipitated solid was collected by filtration, washed with water and air-dried to give the title compound as crystals (6.0 g,

52%). Recrystallization from tetrahydrofuran-hexane gave pale-yellow prism crystals. melting point: 262-263°C.

Reference Example 20

Methyl 2-chloro-4-(3,4-dichlorophenyl)-5-oxazolepropionate

A mixture of methyl 3-[4-(3,4-dichlorophenyl)-2-oxo-4-oxazolin-5-yl]propionate (9.0 g), phosphorus oxychloride (26.2 g) and pyridine (2.25 g) was heated to 100-105°C and stirred for 1 h. The reaction mixture was added dropwise to warm water (100 mL, 30°C) and extracted with ethyl acetate (150 mL × 2). The organic layer was washed with saturated brine (100 mL) and dried over anhydrous magnesium sulfate. The organic layer was concentrated and the residue was subjected to silica gel column chromatography. The title compound was obtained as a yellow oil (5.00g, 52%) from an eluate from ethyl acetate-hexane (1:4, v/v).

NMR($CDCl_3$)δ: 2.76(2H, t, J=7 Hz), 3.20(2H, t, J=7Hz), 3.70(3H, s), 7.49(2H, d, J=1Hz), 7.79(1H, d, J=1Hz).

Reference Example 21

Methyl 4-(3,4-dichlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepropionate

A mixture of methyl 2-chloro-4-(3,4-dichlorophenyl)-5-oxazolepropionate (1.00 g), 2-methylimidazole (0.82 g), potassium carbonate (0.69 g) and N,N-dimethylformamide (20 mL) was stirred at 120°C for 1 h. The reaction mixture was poured into iced water (100 mL) and the precipitated crystals were collected by filtration, washed with water and then with isopropyl ether and air-dried to give the title compound as crystals. Recrystallization from ethyl acetate-isopropyl ether gave pale-yellow prism crystals (0.82 g, 72%). melting point: 116-117°C

Reference Example 22

4-(3,4-Dichlorophenyl)-2-(2-methyl-1-imidazolyl)-5-